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Tranexamic Acid in Knee Surgery Study—A Multicentered, Randomized, Controlled Trial

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ABSTRACT

Background: Postoperative anemia following elective arthroplasty can lead to prolonged hospital stay and delays in rehabilitation and is often poorly tolerated in patients with cardiovascular disease. Tranexamic acid (TXA) has been shown to reduce perioperative blood loss in total knee arthroplasty (TKA). However, questions over its optimal route of administration remain.
Methods: A double-blinded, placebo, multicentered, randomized, controlled trial investigating the efficacy of topical and systemic routes of a single intraoperative dose (1.5 g) of TXA was conducted. Patients undergoing primary, unilateral TKA were screened for eligibility. Eligible patients were consecutively enrolled from 5 New Zealand centers between July 2014 and November 2015. Three prospective groups running in parallel (topical TXA [tTXA], systemic TXA [sTXA], and placebo) were investigated for a primary outcome of estimated perioperative blood loss. An intention-to-treat analysis was used to compare outcomes between the study groups (P value <.05).
Results: One hundred and thirty-four patients across the 5 hospitals were recruited into the study. Estimated blood loss was equivalent in the 2 treatment groups, sTXA (749 mL [95% confidence interval, 637-860]) and tTXA (723 mL [620-826]). Compared to the placebo group (1090 mL [923-1257]), blood loss was significantly lower in both treatment groups ($P = .001$ and $P = .0003$, respectively). There were no significant differences in secondary outcomes, including rates of symptomatic deep vein thrombosis and pulmonary embolism ($P = .759$).
Conclusion: In the setting of elective TKA, a single 1.5-g dose of tTXA given intraoperatively either systemically or topically effectively reduces blood loss without an increase in complications.

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Postoperative anemia following elective arthroplasty can lead to prolonged hospital stay and delays in rehabilitation and is often poorly tolerated in patients with cardiovascular disease [1]. Tranexamic acid (TXA) in arthroplasty is used by many orthopedic surgeons to reduce perioperative blood loss and subsequent transfusion of blood products in elective total hip and knee arthroplasty (THA and TKA) [2,3]. In several reviews, systemic TXA (sTXA) significantly reduces blood loss and transfusion rates, without an increased risk of venous thromboembolism (VTE) [4–6].

Despite evidence for its use in arthroplasty, some surgeons remain cautious over the safety profile of sTXA. Certainly in New

Zealand before the implementation of Enhanced Recovery principles where TXA is encouraged, its use was sporadic and only few surgeons used TXA as part of their routine perioperative care [3]. Similarly, arthroplasty units in the UK have found poor compliance with TXA use [2].

Although TXA, a synthetic derivative of lysine, is responsible for binding reversibly to plasminogen effectively inhibiting clot degradation, it is not clot promoting [7]. Theoretically, there may be an increase in the likelihood of clot formation and this may present an additional risk of VTE in patients who already have multiple risk factors. To reduce thromboembolic risk, surgeons have used TXA as a topical application directly into the surgical field to minimize systemic absorption [8,9]. Additionally, TXA administered topically in TKA has also been reported to reduce swelling which may have the advantage of earlier mobility and less pain [10]. In cardiac surgery, it has been suggested that TXA can reduce inflammation via attenuation of the proinflammatory cascade [11,12].

The purpose of this study was to assess whether topical TXA (tTXA) is effective in reducing blood loss in knee joint replacement surgery compared to sTXA.

Methods

The research reported here is in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement [13]. Ethical approval was obtained from the New Zealand National Health and Disability Ethics Committee (13/CEN/101). The trial was registered at ClinicalTrials.gov (NCT02278263).

Study Design

A double-blinded, placebo, multicentered, randomized, controlled trial was performed investigating the efficacy of topical and systemic routes of a single intraoperative dose (1.5 g) of TXA with 3 prospective groups running in parallel. The sTXA, tTXA, and placebo arms were weighted with a 2:2:1 allocation ratio, respectively.

Participants

From July 2014 to November 2015, patients were recruited from 5 hospitals in New Zealand after study approval at each center. Patients older than 18 years undergoing primary unilateral TKA were eligible to participate in the study. Patients were excluded if they had a history or risk of thrombosis, active thromboembolic disease, refused blood products, known hypersensitivity to TXA or any of its ingredients, complex hematologic disorders requiring manipulation, pregnant and lactating women, taking anticoagulant therapy within 5 days of surgery (warfarin, dabigatran, heparin, rivaroxaban), or had severe renal failure (estimated glomerular filtration rate <29).

Standard Surgical Protocol

Surgery was performed as per each surgeon's routine practice with standardization of potential confounders (Table 1). All patients received a midline incision with a medial parapatellar approach with standard hemostasis techniques. Both conventional and computer-navigated knee arthroplasty were performed. The patellar was selectively resurfaced as per surgeon preference. All components were cemented. All patients received aspirin 150-300 mg/d for 6 weeks following surgery agreed upon by all surgeons. When an intramedullary jig was used, this was plugged with either bone or cement. All but 1 surgeon used cruciate-retaining implants; the single surgeon used posterior-substituting TKAs. Trainee registrars were involved in some of the enrolled surgeries.

Table 1
Surgical Protocol Pertaining to Primary Outcome.

Standardized Aspects of Surgery
Tourniquet inflation to 250-300 mmHg immediately before skin incision
No surgical drains
No adrenaline used as part of high-volume local anesthetic
Tourniquet deflated while crepe bandage being applied
Aspirin 150-300 mg orally for 6 wk
All but a single surgeon used cruciate-retaining implants. The single surgeon used a posterior-stabilized implant.

Anesthetic Protocol

Spinal anesthesia was performed, with or without intravenous sedation. All patients received high-volume local anesthetic (ropivacaine 0.2% diluted in 100-200 mL) to the periarticular tissue.

Postoperative Management

Patients were managed according to the operating surgeon's routine postoperative protocols. Although there were slight intercenter differences with respect to their protocols, each patient was managed according to their standardized, perioperative protocol.

Treatment Protocol

Once the arthrotomy was closed, the study drug was then injected intra-articularly followed by standard closure in layers with absorbable sutures or clips to skin. At the same time the intra-articular study drug was injected, the anesthetist administered the intravenous study medication. The interventions for each group are summarized in Table 2. Study drug preparation was performed on the day of surgery by the theater nurses and attending anesthetist. After allocation, the intra-articular syringe was prepared by the circulating and scrub nurses. This was done in the sterile prescrub area concealed from the surgeon.

The dose of TXA was agreed upon by the authors and based on a systematic literature review of tTXA. Panteli et al demonstrated reduced requirements for allogenic transfusion with doses of $\geq$2 g given topically [14]. Given the theoretical risk of VTE, the authors felt cautious giving these doses intravenously and deemed too high for this route, hence a dose of 1.5 g was chosen.

Table 2
Summary of Intervention Groups.

Group	Intervention
A	Intra-articular[a]: 20 mL of normal saline intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure Intravenous: administration of 20 mL of normal saline intravenously at the same time before release of tourniquet
B	Intra-articular[a]: 1.5 g TXA in 20 mL intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure Intravenous: administration of 20 mL of normal saline (in a 20-mL syringe) intravenously at the same time before release of tourniquet
C	Intra-articular[a]: 20 mL of normal saline intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure Intravenous: administration of 1.5 g TXA intravenously at the same time before release of tourniquet

TXA, tranexamic acid.
[a] All intra-articular study drugs were administered using a single 20-mL syringe via a 20-gauge hypodermic needle.